

HEPARIN SODIUM - heparin sodium injection, solution

Hospira, Inc.

Flexible Plastic Container

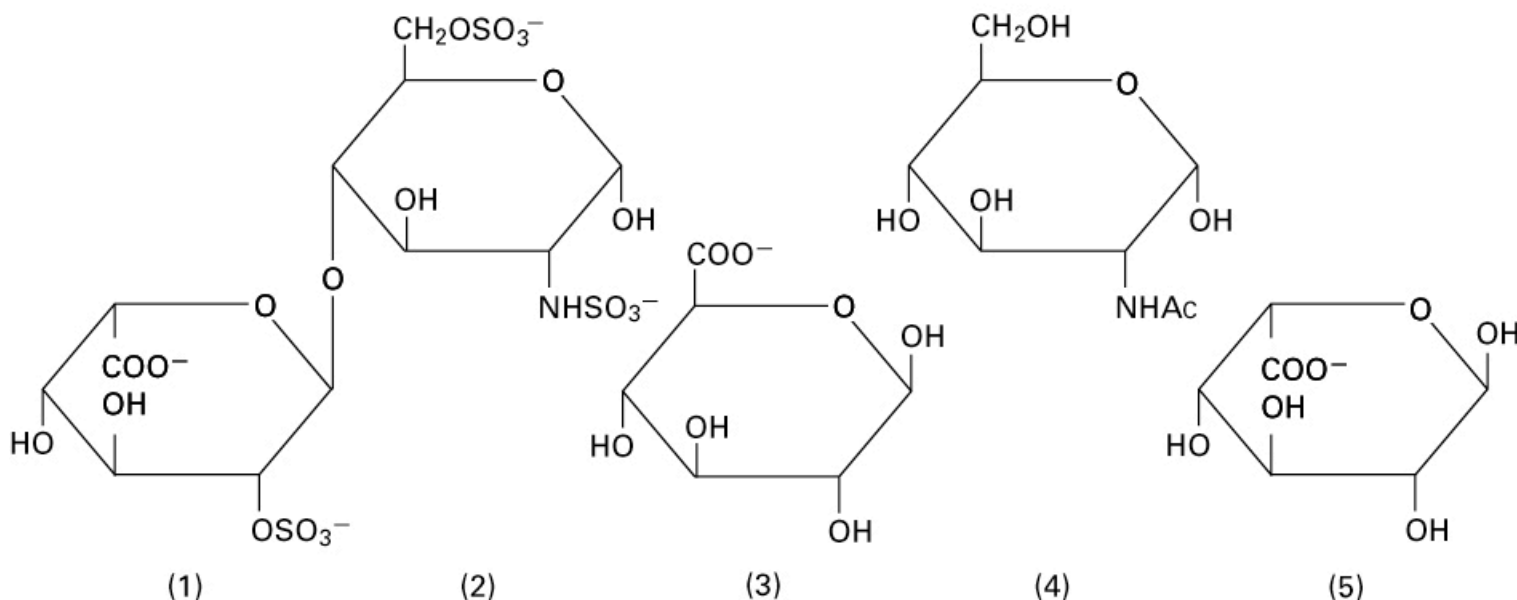
R_x only

DESCRIPTION

Intravenous solutions with heparin sodium (derived from porcine intestinal mucosa) are sterile, nonpyrogenic fluids for intravenous administration. Each 100 mL contains heparin sodium 200 USP Heparin Units; sodium chloride, 0.9 g; citric acid, monohydrate, 40 mg and dibasic sodium phosphate, heptahydrate, 434 mg added as buffers. Each liter contains the following electrolytes: Sodium 186.4 mEq; phosphate (as HPO₄⁼) 32.4 mEq, citrate 5.7 mEq and chloride 154 mEq. Osmolar concentration, 378 mOsmol/liter (calc.); pH 7.0 (5.0 – 7.5).

Heparin Sodium, USP is a heterogenous group of straight-chain anionic mucopolysaccharides, called glycosaminoglycans having anticoagulant properties. Although others may be present, the main sugars occurring in heparin are: (1) α-L-iduronic acid 2-sulfate, (2) 2-deoxy-2-sulfamino-α-D-glucose-6-sulfate, (3) β-D-glucuronic acid, (4) 2-acetamido-2-deoxy-α-D-glucose, and (5) α-L-iduronic acid. These sugars are present in decreasing amounts, usually in the order (2) > (1) > (4) > (3) > (5), and are joined by glycosidic linkages, forming polymers of varying sizes. Heparin is strongly acidic because of its content of covalently linked sulfate and carboxylic acid groups. In heparin sodium, the acidic protons of the sulfate units are partially replaced by sodium ions. The potency is determined by a biological assay using a USP reference standard based on units of heparin activity per milligram.

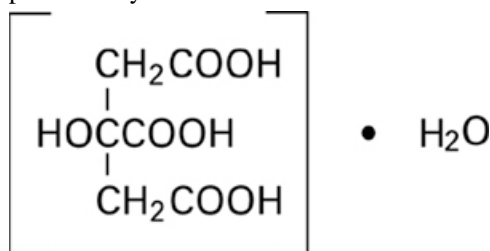
Structure of Heparin Sodium (representative subunits):



Sodium Chloride, USP is chemically designated NaCl, a white crystalline compound freely soluble in water.

Dibasic Sodium Phosphate, USP (Heptahydrate), is chemically designated (Na₂HPO₄•7H₂O), colorless or white granular salt freely soluble in water.

Citric Acid, USP, hydrous (monohydrate) is chemically designated C₆H₈O₇•H₂O, colorless, translucent crystals or white crystalline powder very soluble in water. It has the following structural formula:



Water for Injection, USP is chemically designated H₂O.

The flexible plastic container is fabricated from a specially formulated polyvinylchloride. Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions inside the plastic container also can leach out certain of its chemical components in very small amounts before the expiration period is attained. However, the safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers.

CLINICAL PHARMACOLOGY

Heparin inhibits reactions that lead to the clotting of blood and the formation of fibrin clots both *invitro* and *in vivo*. Heparin acts at multiple sites in the normal coagulation system. Small amounts of heparin in combination with antithrombin III (heparin cofactor) can inhibit thrombosis by inactivating activated Factor X and inhibiting the conversion of prothrombin to thrombin. Once active thrombosis has developed, larger amounts of heparin can inhibit further coagulation by inactivating thrombin and preventing the conversion of fibrinogen to fibrin. Heparin also prevents the formation of a stable fibrin clot in inhibiting the activation of the fibrin stabilizing factor.

Bleeding time is usually unaffected by heparin. Clotting time is prolonged by full therapeutic doses of heparin; in most cases, it is not measurably affected by low doses of heparin.

Patients over 60 years of age, following similar doses of heparin, may have higher plasma levels of heparin and longer activated partial thromboplastin times (APTTs) compared with patients under 60 years of age.

Peak plasma levels of heparin are achieved 2 to 4 hours following subcutaneous administration, although there are considerable individual variations. Loglinear plots of heparin plasma concentrations with time for a wide range of dose levels are linear which suggests the absence of zero order processes. Liver and the reticuloendothelial system are the site of biotransformation. The biphasic elimination curve, a rapidly declining alpha phase ($t_{1/2} = 10\#$) and after the age of 40 a slower beta phase, indicates uptake in organs. The absence of a relationship between anticoagulant half-life and concentration half-life may reflect factors such as protein binding of heparin.

Heparin does not have fibrinolytic activity; therefore, it will not lyse existing clots.

Hypotonic concentrations of sodium chloride are suited for parenteral maintenance of water requirements when only small quantities of salt are desired.

Sodium chloride in water dissociates to provide sodium (Na^+) and chloride (Cl^-) ions. Sodium (Na^+) is the principal cation of the extracellular fluid and plays a large part in the therapy of fluid and electrolyte disturbances. Chloride (Cl^-) has an integral role in buffering action when oxygen and carbon dioxide exchange occurs in the red blood cells. The distribution and excretion of sodium (Na^+) are largely under the control of the kidney which maintains a balance between intake and output.

Water is an essential constituent of all body tissues and accounts for approximately 70% of total body weight.

Average normal adult daily requirements range from two to three liters (1.0 to 1.5 liters each for insensible water loss by perspiration and urine production).

Water balance is maintained by various regulatory mechanisms. Water distribution depends primarily on the concentration of electrolytes in the body compartments and sodium (Na^+) plays a major role in maintaining physiologic equilibrium.

INDICATIONS AND USAGE

Heparin Sodium Injection in 0.9% Sodium Chloride at a concentration of 2 units/mL is indicated as an anticoagulant to maintain catheter patency.

CONTRAINDICATIONS

Heparin sodium should not be used in patients:

With severe thrombocytopenia;

In whom suitable blood coagulation tests — e.g., the whole blood clotting time, partial thromboplastin time, etc. — cannot be performed at appropriate intervals (this contraindication refers to full-dose heparin; there is usually no need to monitor coagulation parameters in patients receiving low-dose heparin);

With an uncontrollable active bleeding state (see WARNINGS), except when this is due to disseminated intravascular coagulation.

WARNINGS

Heparin is not intended for intramuscular use.

Hypersensitivity: Patients with documented hypersensitivity to heparin should be given the drug only in clearly life-threatening situations.

Hemorrhage: Hemorrhage can occur at virtually any site in patients receiving heparin. An unexplained fall in hematocrit, fall in blood pressure, or any other unexplained symptom should lead to serious consideration of a hemorrhagic event.

Heparin sodium should be used with extreme caution in disease states in which there is increased danger of hemorrhage. Some of the conditions in which increased danger of hemorrhage exists are:

Cardiovascular— Subacute bacterial endocarditis. Severe hypertension.

Surgical— During and immediately following (a) spinal tap or spinal anesthesia or (b) major surgery, especially involving the brain, spinal cord, or eye.

Hematologic— Conditions associated with increased bleeding tendencies, such as hemophilia, thrombocytopenia, and some vascular purpuras.

Gastrointestinal— Ulcerative lesions and continuous tube drainage of the stomach or small intestine.

Other— Menstruation, liver disease with impaired hemostasis.

Coagulation Testing: When heparin sodium is administered in therapeutic amounts, its dosage should be regulated by frequent blood coagulation tests. If the coagulation test is unduly prolonged or if hemorrhage occurs, heparin sodium should be discontinued promptly (see OVERDOSAGE).

Thrombocytopenia: Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of 0 to 30%. Mild thrombocytopenia (count greater than 100,000/mm³) may remain stable or reverse even if heparin is continued. However, thrombocytopenia of any degree should be monitored closely. If the count falls below 100,000/mm³ or if recurrent thrombosis develops (see White Clot Syndrome, PRECAUTIONS), the heparin product should be discontinued. If continued heparin therapy is essential, administration of heparin from a different organ source can be reinstituted with caution.

Solutions containing sodium ions should be used with great care, if at all, in patients with congestive heart failure, severe renal insufficiency and in clinical states in which there exists edema with sodium retention.

The intravenous administration of these solutions can cause fluid and/or solute overloading resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary edema.

The risk of dilutional states is inversely proportional to the electrolyte concentrations of administered parenteral solutions. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentrations of such solutions.

In patients with diminished renal function, administration of solutions containing sodium ions may result in sodium retention.

Excessive administration of potassium-free solutions may result in significant hypokalemia.

As the dosage of solutions of heparin sodium must be titrated to individual patient response, additive medications should not be delivered via this solution.

PRECAUTIONS

General:

a. White Clot Syndrome:

It has been reported that patients on heparin may develop new thrombus formation in association with thrombocytopenia resulting from irreversible aggregation of platelets induced by heparin, the so-called "white clot syndrome". The process may lead to severe thromboembolic complications like skin necrosis, gangrene of the extremities that may lead to amputation, myocardial infarction, pulmonary embolism, stroke and possibly death. Therefore, heparin administration should be promptly discontinued if a patient develops new thrombosis in association with thrombocytopenia.

b. Heparin Resistance:

Increased resistance to heparin is frequently encountered in fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, myocardial infarction, cancer and in postsurgical patients.

c. Increased Risk to Older Patients, Especially Women:

A higher incidence of bleeding has been reported in patients, particularly women, over 60 years of age.

Laboratory Tests:

Periodic platelet counts, hematocrits and tests for occult blood in stool are recommended during the entire course of heparin therapy, regardless of the route of administration (see DOSAGE AND ADMINISTRATION).

Drug Interactions:

Oral anticoagulants: Heparin sodium may prolong the one-stage prothrombin time. Therefore, when heparin sodium is given with dicumarol or warfarin sodium, a period of at least 5 hours after the last intravenous dose should elapse before blood is drawn if a valid PROTHROMBIN time is to be obtained.

Platelet inhibitors: Drugs such as acetylsalicylic acid, dextran, phenylbutazone, ibuprofen, indomethacin, dipyridamole, hydroxychloroquine and others that interfere with platelet-aggregation reactions (the main hemostatic defense of heparinized patients) may induce bleeding and should be used with caution in patients receiving heparin sodium.

Other interactions: Digitalis, tetracyclines, nicotine, antihistamines, or I.V. nitroglycerin may partially counteract the anticoagulant action of heparin sodium.

Drug/Laboratory Test Interactions:

Hyperaminotransferasemia: Significant elevations of aminotransferase (SGOT [S-AST] and SGPT [S-ALT]) levels have occurred in a high percentage of patients (and healthy subjects) who have received heparin. Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, rises that might be caused by drugs (like heparin) should be interpreted with caution.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No long-term studies in animals have been performed to evaluate carcinogenic potential of heparin. Also, no reproduction studies in animals have been performed concerning mutagenesis or impairment of fertility.

Pregnancy:

Teratogenic Effects:*Pregnancy Category C.* Animal reproduction studies have not been conducted with heparin sodium or sodium chloride. It is also not known whether heparin sodium or sodium chloride can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Heparin sodium or sodium chloride should be given to a pregnant woman only if clearly needed.

Nonteratogenic Effects: Heparin does not cross the placental barrier.

Nursing Mothers:

Heparin is not excreted in human milk.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use:

A higher incidence of bleeding has been reported in patients over 60 years of age, especially women (see PRECAUTIONS, General and CLINICAL PHARMACOLOGY).

Do not administer unless the solution is clear and seal is intact. Discard unused portion.

ADVERSE REACTIONS

Hemorrhage: Hemorrhage is the chief complication that may result from heparin therapy (see WARNINGS). An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug (see OVERDOSAGE). **It should be appreciated that gastrointestinal or urinary tract bleeding during anticoagulant therapy may indicate the presence of an underlying occult lesion.** Bleeding can occur at any site but certain specific hemorrhagic complications may be difficult to detect:

- Adrenal hemorrhage, with resultant acute adrenal insufficiency, has occurred during anticoagulant therapy. Therefore, such treatment should be discontinued in patients who develop signs and symptoms of acute adrenal hemorrhage and insufficiency. Initiation of corrective therapy should not depend on laboratory confirmation of the diagnosis, since any delay in an acute situation may result in the patient's death.
- Ovarian (corpus luteum) hemorrhage developed in a number of women of reproductive age receiving short- or long-term anticoagulant therapy. This complication if unrecognized may be fatal.
- Retroperitoneal hemorrhage.

Local Irritation: Local irritation, erythema, mild pain, hematoma or ulceration may follow deep subcutaneous (intrafat) injection of heparin sodium. These complications are much more common after intramuscular use, and such use is not recommended.

Hypersensitivity: Generalized hypersensitivity reactions have been reported, with chills, fever and urticaria as the most usual manifestations, and asthma, rhinitis, lacrimation, headache, nausea and vomiting and anaphylactoid reactions, including shock, occurring more rarely. Itching and burning, especially on the plantar site of the feet may occur.

Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of 0 to 30%. While often mild and of no obvious clinical significance, such thrombocytopenia can be accompanied by severe thromboembolic complications such as skin necrosis, gangrene of the extremities that may lead to amputation, myocardial infarction, pulmonary embolism, stroke and possibly death. (See WARNINGS and PRECAUTIONS.)

Certain episodes of painful, ischemic and cyanosed limbs have in the past been attributed to allergic vasospastic reactions. Whether these are in fact identical to the thrombocytopenia associated complications remains to be determined.

Miscellaneous: Osteoporosis following long-term administration of high doses of heparin, cutaneous necrosis after systemic administration, suppression of aldosterone synthesis, delayed transient alopecia, priapism and rebound hyperlipemia on discontinuation of heparin sodium have also been reported.

Significant elevations of aminotransferase (SGOT [S-AST] and SGPT [S-ALT]) levels have occurred in a high percentage of patients (and healthy subjects) who have received heparin.

Reactions which may occur because of the solution or the technique of administration include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation and hypervolemia.

If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures and save the remainder of the fluid for examination if deemed necessary.

OVERDOSAGE

Symptoms: Bleeding is the chief sign of heparin overdosage. Nosebleeds, blood in urine or tarry stools may be noted as the first sign of bleeding. Easy bruising or petechial formations may precede frank bleeding.

Treatment: Neutralization of heparin effect.

When clinical circumstances (bleeding) require reversal of heparinization, protamine sulfate (1% solution) by slow infusion will neutralize heparin sodium. **No more than 50 mg** should be administered, **very slowly** in any 10 minute period. Each mg of protamine sulfate neutralizes approximately 100 USP heparin units. The amount of protamine required decreases over time as heparin is metabolized. Although the metabolism of heparin is complex, it may, for the purpose of choosing a protamine dose, be assumed to have a half-life of about 1/2 hour after intravenous injection.

Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions often resembling anaphylaxis have been reported, the drug should be given only when resuscitation techniques and treatment of anaphylactoid shock are readily available.

For additional information, the labeling of Protamine Sulfate Injection, USP products should be consulted.

In the event of overhydration or solute overload, re-evaluate the patient and institute appropriate corrective measures. See WARNINGS and PRECAUTIONS.

DOSAGE AND ADMINISTRATION

Heparin Sodium is not effective by oral administration and intravenous solutions with heparin sodium should not be given orally. They should be administered by intravenous infusion.

Maintenance of Catheter Patency

Although the rate for infusion of the 2 units/mL formulation is dependent upon the age, weight, clinical condition of the patient, and the procedure being employed, an infusion rate of 3 mL/hour has been found to be satisfactory.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. See PRECAUTIONS.

INSTRUCTIONS FOR USE

To Open

Tear outer wrap at notch and remove solution container.

Preparation for Administration

(Use aseptic technique)

1. Close flow control clamp of administration set.
2. Remove cover from outlet port at bottom of container.
3. Insert piercing pin of administration set into port with a twisting motion until the set is firmly seated. **NOTE:** When using a vented administration set, replace bacterial retentive air filter with piercing pin cover. Insert piercing pin with twisting motion until shoulder of air filter housing rests against the outlet port flange.
4. Suspend container from hanger.
5. Squeeze and release drip chamber to establish proper fluid level in chamber.
6. Attach venipuncture device to set.
7. Open clamp to expel air from set and venipuncture device. Close clamp.
8. Perform venipuncture.
9. Regulate rate of administration with flow control clamp.

WARNING: Do not use flexible container in series connections.

HOW SUPPLIED

Intravenous solutions with heparin sodium are supplied in single-dose containers providing 500 and 1000 mL fluid volumes (List 7620).

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25°C); however, brief exposure up to 40°C does not adversely affect the product.

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